EXHIBIT A

*270 Ore. 375, *; 528 P.2d 522, **;*
*1974 Ore. LEXIS 311, ****

McEWEN, Respondent, v. ORTHO PHARMACEUTICAL CORPORATION et al, Appellants

[NO NUMBER IN ORIGINAL]

SUPREME COURT OF OREGON

270 Ore. 375; 528 P.2d 522; 1974 Ore. LEXIS 311

January 10, 1974, Argued
November 15, 1974

SUBSEQUENT HISTORY: [*1]** Petition for Rehearing Denied December 10, 1974.

PRIOR HISTORY: Appeal from Circuit Court, Multnomah County. Richard J. Burke, Judge.

DISPOSITION: Affirmed.

LEXISNEXIS® HEADNOTES Show

COUNSEL: *Edwin J. Peterson*, Portland, argued the cause for appellant Ortho Pharmaceutical Corp. With him on the brief were Tooze, Kerr & Peterson, Portland, and Souther, Spaulding, Kinsey, Williamson & Schwabe, Portland.

Sheila Birnbaum, New York, New York, argued the cause for appellant Syntex Laboratories. On the brief were Bruce Spaulding, and Souther, Spaulding, Kinsey, Williamson & Schwabe, Portland.

J. Harold Williams, of Michaud, Cranmer, Syrios & Post, Wichita, Kansas, and Roger Tilbury, Portland, argued the cause for respondent. With them on the brief were Bruce J. Rothman, and Martindale, Ruben & Rothman, Portland.

JUDGES: Howell, Justice. O'Connell, Chief Justice, and McAllister, Denecke, * Holman and Bryson, Justices.

* Denecke, J., did not participate in this decision.

OPINION BY: HOWELL

OPINION

[*381] [526]** This is a negligence action involving the liability of a manufacturer of ethical drugs [1] for its alleged failure to make timely, adequate warnings to the medical profession of dangers which the manufacturer **[***2]** knows, or has reason to know, are inherent in the use of its drug.

FOOTNOTES

1 As used herein, an *ethical drug* means a prescription drug as distinguished from a

proprietary or patent drug sold over the counter.

Freda McEwen brought this action against defendants, Ortho Pharmaceutical Corporation and Syntex Laboratories, Inc. (hereinafter Ortho and Syntex, respectively), to recover damages for blindness in her right eye and injuries to her left eye. In her complaint, Mrs. McEwen alleged that each defendant failed to adequately warn the medical profession concerning the dangerous propensities of its oral contraceptive to cause circulatory and visual damage. She further alleged that her combined use of defendants' drugs resulted in ocular injuries. Both defendants appeal from a jury verdict for plaintiff.

Defendants assign a total of 26 errors to the proceedings below, but their principal assignments of error arise from the trial court's denial of defendants' motions for a judgment of involuntary nonsuit and for **[***3]** a directed verdict. In our consideration of the propriety of the trial court's refusal to grant such motions, the plaintiff is entitled to the benefit of every reasonable **[*382]** inference which may be drawn from the evidence; such inferences may be drawn from defendants' as well as plaintiff's evidence. *Scott v. Mercer Steel/Edwards Realty*, 263 Or 464, 466-67, 503 P2d 1242 (1972); *Phillips v. Colfax Co.*, 195 Or 285, 302-03, 243 P2d 276, 245 P2d 898 (1952). Moreover, all evidence must be interpreted in the light most favorable to the plaintiff, and it is beyond our power to weigh or evaluate conflicting evidence. *Schweiger et ux v. Solbeck et ux*, 191 Or 454, 471, 230 P2d 195, 29 ALR3d 435 (1951). *See also Kraxberger v. Rogers*, 231 Or 440, 449, 373 P2d 647 (1962); Oregon Constitution, Amended Article VII, § 3.

Our sole concern is whether there was sufficient evidence to submit the case to the jury. The validity of the trial court's determinations depends upon whether there was substantial evidence that each defendant failed to adequately warn the medical profession of the pertinent dangerous propensities of its oral contraceptive and, if so, whether there **[***4]** was also substantial evidence that this failure caused plaintiff's injuries. With this perspective, we set forth **[**527]** the factual chronology which produced this litigation.

Defendants' oral contraceptives involved herein are chemically identical. Syntex calls its product "Norinyl," while "Ortho-Novum" is the trade name used by Ortho. Each contraceptive consists of 2 milligrams of the progestogen norethindrone and 0.1 milligram of the estrogen mestranol. Syntex and Ortho have coordinated their efforts to discover the dangerous propensities of this compound by sharing information, undertaking joint animal studies, and exchanging reports of adverse reactions.

Mrs. McEwen began using Norinyl on December **[*383]** 3, 1966. In the following months she experienced severe headaches, nausea, falling hair, swollen ankles and feet, and a constant backache. Beginning in July, 1967, plaintiff discontinued her use of the drug for three months, and during this period these symptoms subsided. She resumed her use of Norinyl in October. Within a short time she began to experience difficulty with her vision. In November, 1967, plaintiff called Kaiser Hospital in Portland and reported **[***5]** that she was losing the sight in her right eye. The following month she began to cough up blood. On December 20, 1967, an examining physician at Kaiser changed plaintiff's prescription from Norinyl to Ortho-Novum oral contraceptives.

Dr. Sutton, an ophthalmologist with Kaiser Hospital, examined plaintiff on January 2, 1968. He noted that Mrs. McEwen's eyes did not focus properly. He also found her eyeballs to be bulging and diagnosed the condition as nearsightedness. He observed no other abnormalities in her eyes at that time. Plaintiff informed Dr. Sutton that she was taking Ortho-Novum.

About 11 months later, on December 5, 1968, plaintiff noticed two vivid black lines come across the field of vision in her right eye. She blinked, and the lines disappeared. Similar lines

appeared a few days later, followed by black dots which seemed to fill her right eye. Dr. Neville, an ophthalmologist, examined Mrs. McEwen on December 9, 1968, and observed a growth of abnormal new blood vessels extending out from the retina [2] into the vitreous [3] of **[*384]** her right eye. Dr. Neville further noted a vitreous hemorrhage in plaintiff's right eye. On December 11, 1968, Dr. Sutton **[***6]** again examined plaintiff, finding retinal hemorrhages and essentially confirming Dr. Neville's diagnosis.

FOOTNOTES

[2] Simply defined, the retina is the inside lining of the back of the eye. Stedman's Medical Dictionary 1093-94 (Third unabr. lawyers ed 1972).

[3] The vitreous is "the colorless, transparent gel filling the posterior four-fifths of the eyeball between the retina and the crystalline lens." *Id.* at 1401.

Mrs. McEwen noticed a change in the vision in her left eye on December 21, 1968, which she described as "streaks or looking through gelatin." Dr. Burns of the University of Oregon Medical School advised the plaintiff to discontinue her use of oral contraceptives and she did not take Ortho-Novum after December 22, 1968. [4] To stop the hemorrhaging, Dr. Burns performed photocoagulation operations on plaintiff's right eye. [5] Later, Dr. McPherson, a retinal specialist, photocoagulated Mrs. McEwen's left eye.

FOOTNOTES

[4] Plaintiff testified that she last took a birth control pill on December 25, 1968, but alleged in her complaint that she discontinued her use of Ortho-Novum on December 22, 1968. **[***7]**

[5] Photocoagulation is a process in which an intense beam of light is directed toward the retina of the eye, producing a burn, or coagulation. As the coagulation hardens it produces an adhesive scar. One use of photocoagulation is to obliterate fragile, abnormal blood vessels which can otherwise result in hemorrhaging.

Plaintiff's right eye is totally and permanently blind. Her left eye now tires more easily than before and bears the scars of photocoagulation.

With these facts in mind, we proceed to the legal issues raised by this appeal. Plaintiff's sole theory of recovery in this negligence action is founded upon the alleged **[**528]** failure of defendants to adequately warn the medical profession of the dangerous propensities of their oral contraceptives. Therefore, it was for the court to initially determine "whether the defendant owed any duty whatsoever to the plaintiff with respect to the type of harm suffered by the plaintiff **[*385]** * * *." *Dewey v. A. F. Klaveness & Co.*, 233 Or 515, 541, 379 P2d 560 (1963) (O'Connell, J., concurring). [6] Next, it was incumbent upon **[***8]** plaintiff to prove that there had been a breach of duty by each defendant. Plaintiff finally had to prove that the negligent acts or omissions of each defendant had been a substantial factor in physically causing the damage of which she complained. [7]

FOOTNOTES

[6] *See* Mezyk v. National Repossessions, 241 Or 333, 405 P2d 840 (1965); Prosser, Torts 289, § 45 (4th ed 1971).

[7] "Causation in fact" is unrelated to "proximate" or "legal" cause, concepts which have been discarded by this court. Kuhns v. Standard Oil Co., 257 Or 482, 478 P2d 396 (1971); Babler Bros. v. Pac. Intermountain, 244 Or 459, 415 P2d 735 (1966); Hills v. McGillvrey, 240 Or 476, 402 P2d 722 (1965). All questions relevant in setting the limits of liability for conduct which is, in a physical sense, a substantial cause of an injury are to be considered in resolving the issue of negligence. Eliason (Jones) v. United Amusement, 264 Or 114, 121, 504 P2d 94 (1972) (Denecke, J., concurring); Stewart v. Jefferson Plywood Co., 255 Or 603, 469 P2d 783 (1970); Dewey v. A.F. Klaveness & Co., 233 Or 515, 519, 379 P2d 560 (1963) (O'Connell, J., concurring).

[*9]** We will first examine the scope of defendants' duty.

I. DEFENDANTS' DUTY TO WARN PLAINTIFF'S DOCTORS

There is no question here of any defect in the manufacture of defendants' oral contraceptives, nor of their efficacy when taken as prescribed. It is well settled, however, that the manufacturer of ethical drugs bears the additional duty of making timely and adequate warnings to the medical profession of any dangerous side effects produced by its drugs of which it knows, or has reason to know. E.g., *Sterling Drug, Inc. v. Cornish*, 370 F2d 82 (8th Cir 1966); *Parke-Davis & Co. v. Stromsodt*, 411 F2d 1390 (8th Cir 1969); *Stevens v. Parke, Davis & Co.*, 9 Cal 3d 51, 107 Cal Rptr 45, 507 P2d 653 (1973); *Love v. Wolf*, 226 Cal **[*386]** App 2d 378, 38 Cal Rptr 183 (1964); *Krug v. Sterling Drug, Inc.*, 416 SW2d 143 (Mo Sup Ct 1967); *see* 2 Restatement (Second) of Torts 300, § 388 (1965). [8]

FOOTNOTES

[8]

"§ 388. Chattel Known to be Dangerous for Intended Use

"One who supplies directly or through a third person a chattel for another to use is subject to liability to those whom the supplier should expect to use the chattel with the consent of the other or to be endangered by its probable use, for physical harm caused by the use of the chattel in the manner for which and by a person for whose use it is supplied, if the supplier

"(a) knows or has reason to know that the chattel is or is likely to be dangerous for the use for which it is supplied, and

"(b) has no reason to believe that those for whose use the chattel is supplied will realize its dangerous condition, and

"(c) fails to exercise reasonable care to inform them of its dangerous condition or of the facts which make it likely to be dangerous." 2 Restatement (Second) of Torts 300, § 388 (1965).

[*10]** The duty of the ethical drug manufacturer to warn is limited to those dangers which the manufacturer knows, or has reason to know, are inherent in the use of its drug. However, the drug manufacturer is treated as an expert in its particular field, and is under a "continuous duty * * * to keep abreast of scientific developments touching upon the

manufacturer's product and to notify the medical profession of any additional side effects discovered from its use." *Schenebeck v. Sterling Drug, Inc.*, 423 F2d 919, 922 (8th Cir 1970); *accord* *O'Hare v. Merck & Co.*, 381 F2d 286, 291 (8th Cir 1967). The drug manufacturer's duty to warn is, therefore, commensurate not only with its actual knowledge gained from research and adverse reaction reports but also with its **[**529]** constructive knowledge as measured by scientific literature and other available means of communication.

Although the duty of the ethical drug manufacturer **[*387]** is to warn the doctor, rather than the patient, [9] the manufacturer is directly liable to the patient for a breach of such duty. *See* *Schenebeck v. Sterling Drug, Inc.*, supra; *Love v. Wolf*, supra. The manufacturer's compliance with this duty **[***11]** enables the prescribing physician to balance the risk of possible harm against the benefits to be gained by the patient's use of that drug. Moreover, as observed by the court in *Sterling Drug, Inc. v. Cornish*, supra 370 F2d at 85:

> "* * * [T]he purchaser's doctor is a learned intermediary between the purchaser and the manufacturer. If the doctor is properly warned of the possibility of a side effect in some patients, and is advised of the symptoms normally accompanying the side effect, there is an excellent chance that injury to the patient can be avoided. This is particularly true if the injury takes place slowly * * *."

FOOTNOTES

[9] The application of this rule to drugs such as oral contraceptives has not been without criticism. *See* Comment, Liability of Birth Control Pill Manufacturers, 23 Hastings J 1526, 1538 (1972); *cf.* Davis v. Wyeth Laboratories, Inc., 399 F2d 121 (9th Cir 1968).

Although the ethical drug manufacturer's duty to warn has been discussed most often with reference to the **[***12]** prescribing physician, the above reasoning applies with equal force to the treating physician. It is especially important that the treating doctor receive the manufacturer's warnings where it is impossible to predict in advance whether a particular patient is apt to suffer adverse effects from a drug, since the treating doctor may be more likely to observe the actual symptoms of the drug's untoward consequences. If the prescribing physician is entitled to make an informed choice in deciding whether the patient should begin taking a prescription drug, it follows that a treating physician should have the same information **[*388]** in making his decision as to whether the patient should stop taking that drug.

The duty of the ethical drug manufacturer to warn extends, then, to all members of the medical profession who come into contact with the patient in a decision-making capacity. To satisfy this duty, the manufacturer must utilize methods of warning which will be reasonably effective, taking into account both the seriousness of the drug's adverse effects and the difficulties inherent in bringing such information to the attention of a group as large and diverse as the medical **[***13]** profession. *See* *Sterling Drug, Inc. v. Yarrow*, 408 F2d 978 (8th Cir 1969). The warning should be sufficient to apprise the general practitioner as well as the "unusually sophisticated medical man" of the dangerous propensities of the drug. *Parke-Davis & Co. v. Stromsodt*, 411 F2d 1390, 1400 (8th Cir 1969). In short, "it is incumbent upon the manufacturer to bring the warning home to the doctor." Rheingold, *Products Liability -- The Ethical Drug Manufacturer's Liability*, 18 Rutgers U L Rev 947, 993 (1964).

It has been suggested, however, that the manufacturer of a prescription drug should be under no duty to warn the medical profession that its product is dangerous when used by certain allergic or hypersensitive users. [10] It is unreasonable, so the argument runs, to

impose upon the manufacturer a duty to warn doctors **[*389]** of **[**530]** dangers threatening a statistically insignificant number of users. We find this argument unpersuasive.

FOOTNOTES

[10] The practical application of the "idiosyncratic reaction" defense may present serious problems:

> "* * * [I]n many cases it is medically undetermined whether a type of reaction is to be regarded as idiosyncratic or not, and in many other cases it is impossible to ascertain the specific nature of the user's reaction. * * *" Rheingold, *Products Liability -- The Ethical Drug Manufacturer's Liability*, 18 Rutgers U L Rev 947, 1005-06 (1964).

[*14]** In the field of negligence the duty to warn is limited to those dangerous propensities of the drug of which the manufacturer knows, or has reason to know. If allergic reactions are harder to anticipate, this should be taken into account in evaluating the manufacturer's knowledge. It must be remembered that the negligence liability of the ethical drug manufacturer is restricted to those dangers which *are* foreseeable. [11]

FOOTNOTES

[11] As stated in Stewart v. Jefferson Plywood Co., supra n. 7, 255 Or at 609:

> "[O]ne is negligent only if he, as an ordinarily reasonable person, ought reasonably to foresee that he will expose another to an unreasonable risk of harm."

Furthermore, to simply conclude that it is unreasonable to impose liability where the known danger threatens only a statistically small percentage of the drug's users is to beg the very question of negligence. The size of the class of endangered persons is one -- albeit only one -- of the factors to be considered in deciding whether the **[***15]** manufacturer's warnings were, in fact, reasonable.

The ethical drug manufacturer is, then, subject to a duty to warn the medical profession of untoward effects which the manufacturer knows, or has reason to know, are inherent in the use of its drug. [12] *Sterling Drug, Inc. v. Cornish*, supra 370 F2d 82; *Parke-Davis & Co. v. Stromsodt*, supra 411 F2d 1390; *Basko v. Sterling Drug, Inc.*, 416 F2d 417 (2d Cir 1969); *Love v. Wolf*, supra 226 Cal App 2d 378; *Krug v. Sterling* **[*390]** *Drug, Inc.*, supra 416 SW2d 143; *cf. Davis v. Wyeth Laboratories, Inc.*, 399 F2d 121 (9th Cir 1968). *See also Wright v. Carter Products, Inc.*, 244 F2d 53 (2d Cir 1957); *Hungerholt v. Land O'Lakes Creameries, Inc.*, 209 F Supp 177 (D Minn 1962), aff'd 319 F2d 352 (8th Cir 1963); *Gerkin v. Brown & Sehler Co.*, 177 Mich 45, 143 NW 48 (1913). *But see Winthrop Laboratories Division of Sterling Drug, Inc. v. Crocker*, 502 SW 2d 850 (Tex Civ App 1973).

FOOTNOTES

[12] A contrary result is not dictated by Cochran v. Brooke, 243 Or 89, 409 P2d 904 (1966), in which we refused to impose absolute liability upon the ethical drug manufacturer for unanticipated adverse effects.

[*16]** II. WAS THERE EVIDENCE OF BREACH OF DEFENDANTS' DUTY?

Having established that the manufacturer of a prescription drug is under a duty to give adequate and timely warnings to the medical profession of any dangerous side effects of that drug of which the manufacturer has actual or constructive knowledge, we turn to the instant record and consider the question of whether there was sufficient evidence to permit the jury to find that defendants herein failed to satisfy that duty.

A. Evidence Considered by the Jury Tending to Establish Each Defendant's Knowledge of the Dangerous Propensities of Its Oral Contraceptive Related to Plaintiff's Injuries

Because the ethical drug manufacturer has only the duty to warn the medical profession of those adverse effects of which it knows, or has reason to know, the adequacy of the warnings given by each defendant depends upon the actual and constructive knowledge of that defendant before and during the period in which Mrs. McEwen used its drug. For Syntex, the relevant interval began on December 3, 1966, when plaintiff first took Norinyl, and ended on December 20, 1967, when she changed to Ortho-Novum oral contraceptives. [13] **[*391]** **[***17]** From that date, plaintiff used Ortho-Novum until approximately December 22, 1968, and this is the relevant time span with reference to Ortho's knowledge.

FOOTNOTES

[13] The fact that plaintiff discontinued her use of Norinyl from July 1967 until October 1967 is unrelated to the determination of the relevant period of time in which the knowledge of Syntex is to be considered.

[531]** Before discussing the specific items of evidence considered by the jury, we reiterate that the Norinyl and Ortho-Novum pills taken by plaintiff were chemically identical and that the defendants shared information concerning adverse reactions resulting from use of these drugs.

Numerous studies, reports and other documents were admitted into evidence and discussed by the expert witnesses. Some of these materials support Mrs. McEwen's contention that defendants knew, or should have known, of the dangerous propensities of their oral contraceptives during the time plaintiff was using them.

Dr. Wendel, plaintiff's expert witness, [14] testified **[***18]** **[*392]** that three studies were undertaken in Great Britain during 1965-66 to determine whether a cause-and-effect relationship existed between the use of oral contraceptives and thrombosis, thromboembolism and other related vascular diseases. On cross-examination, Dr. Wendel testified that a preliminary report stating the results of these studies was published in the British Medical Journal on May 6, 1967, [15] and that this preliminary report was the "final conclusive convincing evidence" of a cause-and-effect relationship between the ingestion of oral contraceptives and such disorders. [16] Each defendant is held to have constructive knowledge of this report. *O'Hare v. Merck & Co.*, supra 381 F2d at 291.

FOOTNOTES

14 Defendants contend that Dr. Wendel was unqualified to testify as an expert. Dr. Wendel graduated from medical school in Germany in 1939, practiced medicine for a short time, and then specialized in pharmacology. Thereafter he was employed by a pharmaceutical company in the United States to conduct or supervise the testing of various drugs. Subsequently he was employed by various other pharmaceutical companies to do research, write package inserts, and perform assorted other functions related to research supervision and the sale of drugs. At the time of the trial, Dr. Wendel was an associate professor of pharmacology at the University of Oregon Medical School. He was not licensed to practice medicine anywhere in the United States.

In Wulff v. Sprouse-Reitz Co., 262 Or 293, 305, 498 P2d 766 (1972), we reiterated the rule that the competency of a witness to testify as an expert is a preliminary matter within the sound discretion of the trial judge. We noted that the question of whether the witness called is the best expert witness on the particular subject is a matter bearing on the weight to be given the witness's testimony and not on the qualification of the witness. In the instant case the trial court did not abuse its discretion. **[***19]

15 Medical Research Council, Risk of Thromboembolic Disease in Women Taking Oral Contraceptives, 2 British Medical J. 355-359 (1967).

16 Later British reports published in April 1968 confirmed the conclusions of the preliminary report and indicated that the risk of venous thrombosis, pulmonary embolism and cerebral thrombosis is actually increased about eight times by the use of oral contraceptives. Inman & Vessey, 2 British Medical J. 193 (1968); Vessey & Doll, 2 British Medical J. 199 (1968). The British findings led an Advisory Committee of the Food and Drug Administration to conclude that "these studies together establish an etiologic relation between thromboembolic disorders and the use of oral contraceptives." Advisory Committee on Obstetrics and Gynecology, Food and Drug Administration, Second Report on the Oral Contraceptives 6 (Aug. 1969).

Another important investigation was the cooperative two-year oral drug safety study conducted by Ortho and Syntex. The purpose of this study was to determine the effects on rats of norethindrone and mestranol (the components of defendants' **[***20]** oral contraceptives). An interim report received in evidence reported **[*393]** the findings with reference to rats treated from December 31, 1965, to March 31, 1966. Dr. Wendel testified that this interim report indicated that defendants' oral contraceptives injured the rats' eyes, and that "some of the lesions resemble, to me, very much the lesions found in the retinas of Mrs. McEwen." One of the rats treated with norethindrone experienced a local retinal hemorrhage.

Also received in evidence was a 1965 article 17 stating the results of an inquiry **[**532]** into the occurrence of ocular disorders in women using oral contraceptives. Upon cross-examination, Dr. Wendel testified with reference to this report:

> "Q Do you know of any article by any doctor that implicates oral contraceptives prior to January 1, 1969 with retinal hemorrhages or retinal occlusions?
>
> "A The Walsh article, ja.
>
> "Q The Walsh article does?
>
> "A As I studied it, among his sixty or some patients there are nine which had ocular lesions which, in my opinion, resembled changes found in Mrs. McEwen."

FOOTNOTES

17 Walsh, Clark, Thompson & Nicholson, Oral Contraceptives and Neuro-Ophthalmologic Interest, 74 Archives of Ophthalmology 628 (1965).

[*21]** In addition to these studies, there was further evidence tending to show that each manufacturer had some knowledge during the relevant time periods of a connection between the use of its oral contraceptive and injuries such as those suffered by plaintiff. For example, the Norinyl package inserts 18 in effect during **[*394]** the period in which plaintiff took that drug included the following warnings: 19

> "CONTRAINDICATIONS 20
>
> "1. * * * At this time Norinyl is not recommended in patients with thrombophlebitis or with a history of thrombophlebitis or pulmonary embolism.
>
> "* * *
>
> "WARNING
>
> "Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn."

The above-quoted admonition concerning loss of vision was added as a "precaution" to the November 1967 Ortho-Novum package insert.

FOOTNOTES

18 The "package insert" is a leaflet containing information about the particular drug which it accompanies. It is given to the physician, not the patient. **[***22]**

19 See IIB *infra* for our discussion of the adequacy of defendants' warnings.

20 A "contraindication" is "any special symptom or circumstance that renders the use of a remedy or the carrying out of a procedure inadvisable." Stedman's Medical Dictionary, supra n. 2 at 283.

An additional precaution was added to the Ortho-Novum package insert dated December 1967:

> "10. Because of the occasional occurrence of thrombophlebitis and pulmonary embolism in patients taking oral contraceptives, the physician should be alert to the earliest manifestations of the disease."

The same Ortho-Novum insert noted thrombophlebitis, pulmonary embolism and neuro-ocular lesions among the side effects observed in patients receiving oral contraceptives. That insert also stated that the clinical laboratory results of coagulation tests indicated **[*395]** that Ortho-Novum affected various characteristics of blood clotting.

Finally, the June 1968 package insert for Ortho-Novum revealed the conclusion of the studies conducted in Great Britain and reported in April 1968 that "there is a seven **[***23]** to tenfold increase in mortality and morbidity due to thromboembolic diseases in women taking oral contraceptives." The insert further warned the physician to be alert to the earliest manifestation of thrombotic disorders, including retinal thrombosis, and to discontinue the drug immediately if such disorders occurred or were suspected. This insert also stated that "available evidence is suggestive of an association" between the use of Ortho-Novum and "[n]euroocular lesions, e.g., retinal thrombosis * * *."

Viewing all the testimonial and documentary evidence in its entirety, there was substantial evidence that each defendant knew, or should have known, that its oral contraceptive had a dangerous propensity to cause the kind of harm suffered by plaintiff. [21] This **[*396]** is not to say that defendants **[**533]** did not produce substantial evidence tending to prove that they did *not* have such knowledge during the relevant times. [22] Our sole function, however, has been completed by our determination that reasonable men might differ upon the point. It was for the trier of fact to resolve the conflict.

FOOTNOTES

[21] The foreseeability of neither the precise injury which plaintiff complains of nor the exact manner of its occurrence is a prerequisite of defendants' liability. Rather, negligence liability is "confined to harms actually resulting that are of the general kind to be anticipated from the conduct and * * * to situations in which the person harmed is one of the general class threatened." 1 Harper & James, The Law of Torts, Introduction at xl (1956). Stewart v. Jefferson Plywood Co., supra n. 7, 255 Or at 608-09. Thus we have held that "it is not necessary that the defendants anticipate the precise consequences of their act." Danner v. Arnsberg, 227 Or 420, 423, 362 P2d 758 (1961).

A question similar to that before us was raised in Stewart v. Jefferson Plywood Co., supra at 609-10:

> "* * * [W]hether plaintiff's injury and the manner of its occurrence was so highly unusual that we can say as a matter of law that a reasonable man, making an inventory of the possibilities of harm which his conduct might produce, would not have reasonably expected the injury to occur. Stated in another way, the question is whether the circumstances are out of the range within which a jury could determine the injury was reasonably foreseeable."

[*24]**

[22] For example, the report containing the final results and conclusions of the Ortho-Syntex cooperative rat study was introduced by defendants and it tended to contradict the conclusions of Dr. Wendel based on the preliminary report. Numerous other conflicts appear in the twelve volumes of transcript.

B. Adequacy of the Warnings

With reference to the adequacy of defendants' warnings, the precise issue before us may be stated thus: Was there sufficient evidence for the trial court to permit the jury to decide whether reasonable warnings were given to the medical profession by each defendant concerning the pertinent dangers which that defendant knew, or should have known, were inherent in the use of its drug? We conclude that there was substantial evidence that the warnings of each defendant were inadequate and that the court properly allowed the jury to

resolve the negligence question.

We reach this conclusion by superimposing the warnings actually given over the dangers which were foreseeable by defendants. Although there are numerous methods available to the ethical drug manufacturer **[***25]** to communicate with the medical profession, [23] plaintiff **[*397]** and both defendants have focused primarily on the warnings in the relevant package inserts. Since neither defendant contends that it gave more complete information to doctors through any other means, we, too, will emphasize the cautionary instructions found in the inserts.

FOOTNOTES

[23] Written warnings can be conveyed not only through the manufacturer's labels and package inserts, but also by means of a "Dear Doctor" letter, a communication sent by the manufacturer to all practicing physicians in the United States, informing them about the characteristics or performance of a particular drug. Advertising is also conducted through drug manuals such as the Physicians' Desk Reference. In addition, drug manufacturers can supplement their written warnings by utilizing their "detail men," who personally call on individual doctors in order to promote their employers' drugs.

However, before examining these warnings, we shall discuss defendants' contention **[***26]** that, as a matter of law, an ethical drug manufacturer discharges its duty to warn the medical profession merely by obtaining approval of its labeling from the Food and Drug Administration. Under this theory, the drug manufacturer could not be held liable if its warnings were commensurate with those required by the FDA, regardless of the scope of the manufacturer's knowledge of the adverse effects of its drug.

Defendants rely chiefly upon the following language in *Lewis v. Baker*, 243 Or 317, 324, 413 P2d 400 (1966), to support this theory:

> "* * * We hold that * * * a drug, properly tested, *labeled with appropriate warnings*, approved by the Food and Drug Administration, and marketed properly under federal regulation, is, as **[**534]** a matter of law, a reasonably safe product. * * *" (Emphasis ours.)

Viewed in the context of the entire *Lewis* opinion, it is not clear that satisfaction of the requirement of "appropriate warnings" was to be achieved by mere **[*398]** compliance with the demands of the FDA. In any event, upon closer examination of the question, [24] we agree with the Supreme Court of California that "[t]he warnings required by such **[***27]** agencies may be only minimal in nature and when the manufacturer or supplier knows of, or has reason to know of, greater dangers not included in the warning, its duty to warn may not be fulfilled." *Stevens v. Parke, Davis & Co.*, supra 9 Cal 3d at 65. We hold that the warnings given by an ethical drug manufacturer may be found inadequate, "[a]lthough all of the government regulations and requirements have been satisfactorily met in the production and marketing of [the drug], and in the changes made in the literature * * *." *Yarrow v. Sterling Drug, Inc.*, 263 F Supp 159, 162 (D SD 1967), aff'd 408 F2d 978 (8th Cir 1969); *accord Stromsodt v. Parke-Davis & Co.*, 257 F Supp 991 (D ND 1966), aff'd 411 F2d 1390 (8th Cir 1969). *See also Alman Brothers Farm & Feed Mill, Inc. v. Diamond Laboratories, Inc.*, 437 F2d 1295 (5th Cir 1971). *Lewis v. Baker*, supra, insofar as it conflicts with this principle, is expressly overruled.

FOOTNOTES

[24] *See generally* Merrill, *Compensation for Prescription Drug Injuries*, 59 Va L Rev 1, 1-29 (1973); Rheingold, *Products Liability -- The Ethical Drug Manufacturer's Liability*, supra n. 10, at 950-70.

[*28]** Defendants, however, imply that the adequacy and timeliness of their package insert warnings were beyond their control, since the warnings were written by the FDA and required by federal law to be included in the inserts. Defendants overlook that portion of the Code of Federal Regulations specifically related to changes in drug labeling and advertising which notify the medical profession of a drug's untoward effects:

> "* * *
>
> **[*399]** "(d) Changes of the following kinds * * * should be placed into effect at the earliest possible time:
>
> "(1) The addition to package labeling, promotional labeling, and prescription drug advertising of additional warning, contraindication, side-effect, and precaution information.
>
> "(2) The deletion from package labeling, promotional labeling, and drug advertising of false, misleading, or unsupported indications for use or claims for effectiveness.
>
> "* * *.
>
> "(e) It will be the policy of the Food and Drug Administration to take no action against a drug or applicant solely because changes of the kinds described in paragraph (d) of this section are placed in effect by the applicant prior to his receipt of a written notice of approval * * *." **[***29]** 21 C.F.R. § 130.9 (d), (e) (effective Jan. 30, 1965).

With reference to this amended version of 21 C.F.R. § 130.9, the following conclusion has been drawn:

> "Prior to [the January 30, 1965] amendment [of § 130.9], the drug manufacturer could argue that the timeliness and the adequacy of the warning in a 'Dear Doctor' letter was beyond its control -- the FDA dictated when the letter would be sent and the final form that the warning would take * * *. In light of the above regulatory amendment [§ 130.9 (d), (e)], the drug company should not be permitted to shift responsibility for the timeliness and the adequacy of warning letters to the FDA." 3 L. Frumer & M. Friedman, Products Liability 263-64, § 33.01 (3)(c) (1960).

Compliance with federal law did not prevent defendants from giving timely written warnings to the **[*400]** medical profession, either **[**535]** by means of "Dear Doctor" letters or through changes in their package inserts. [25]

FOOTNOTES

[25] In addition to written warnings, other means of notifying the medical profession of newly-discovered adverse effects were available to defendants. Drug manufacturers often employ "detail men" who periodically visit physicians to promote the use of their employers' products. These representatives could also give warnings. *See* Yarrow v. Sterling Drug, Inc., 263 F Supp 159 (D SD 1967), aff'd 408 F2d 978 (8th Cir 1969).

[*30]** Moving to the adequacy of the warnings made by the respective defendants in their package inserts, the only inserts relevant to the liability of each defendant are those which were operative when that defendant's oral contraceptive was prescribed for and used by Mrs. McEwen. The warnings given by each defendant will be considered separately.

> *Syntex* Warnings on Package Inserts from 12-3-66 when Plaintiff First Took *Norinyl* through 12-20-67 when Plaintiff Last Took *Norinyl*

The relevant warnings made by Syntex are found on the Norinyl package insert dated September 1966, which was superseded only after plaintiff ceased using that drug. Under the heading, "side effects," on this insert, Syntex stated that "the side reactions reported consisted mainly of changes in the menstrual cycle, symptoms resembling early pregnancy, weight gain, nausea, and a few minor, generally transient, subjective complaints." Under the caption "contraindications," Syntex added that "[e]xisting evidence does not support a causal relationship between the use of Norinyl and the development of thromboembolism." The section entitled "laboratory analyses" suggested that there was no **[***31]** significant increase in the risk of thromboembolic death associated with the use of oral contraceptives. The cumulative effect of these "warnings" was a definite assurance that no risk of thrombotic **[*401]** disorders was connected to the use of Norinyl, contrary to the defendants' actual knowledge.

The September 1966 Norinyl package insert also contained the following cautionary language:

> "WARNING
>
> "Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn."

Dr. Wendel testified that this warning was in fact no warning at all. [26] He observed that retinal vascular lesions [27] are generally irreversible injuries which leave permanent damage, and concluded:

> "To label [the above-quoted statement] warning **[*402]** is, to me, a misnomer because it **[**536]** is not an advance notice of something which may come. What this paragraph says is to do certain things after something has happened already."

To make a homely analogy, the disputed warning **[***32]** advises that the barn door should be closed after the horses have fled. By failing to notify the medical profession that Norinyl *could cause* retinal vascular disorders, and by advising that the drug was to be permanently discontinued only after an irreversible injury had been suffered by the patient, this warning did not enable plaintiff's doctors to take corrective action in time to prevent her blindness.

FOOTNOTES

26 Defendants contend that the adequacy of their warnings was not a proper subject for expert testimony. We disagree. As observed by Mr. Justice Holman in Koch v. Southern Pacific Co., 266 Or 335, 341, 513 P2d 770 (1973):

> "The factor which determines if a subject is a proper one for expert testimony is whether the answer of an expert can be of appreciable help to the jury. *Sandow v. Weyerhaeuser Co.*, 252 Or 377, 380, 449 P2d 426 (1969). It depends upon whether the subject is such that the expertise of the witness gives him a special insight superior to that of the average juror. * * *"

It is incumbent upon the ethical drug manufacturer to reasonably notify the medical profession, not the public, of all available scientific evidence concerning the risks inherent in its drug. The warnings given by defendants were not directed to Mrs. McEwen, but to her doctors. Dr. Wendel's opinion as to the adequacy of defendants' warnings could have been of substantial assistance to the trier of fact in its resolution of this difficult technical question. This is no less true merely because the matter commented upon was one of the principal or "ultimate" questions of fact to be decided by the jury. Ritter v. Beals, 225 Or 504, 358 P2d 1080 (1961); Welter, Adm'x v. M & M Woodworking Co., 216 Or 266, 338 P2d 651 (1959). **[***33]**

27 Dr. Wendel defined the term "retinal vascular lesion" as being "a comprehensive term which includes various pathological changes of the vessels of the retina, such as occlusion of the vessels, thrombosis, inflammation, formation of new vessels, hemorrhage."

Although the preliminary report of the British studies was published on May 6, 1967, reporting evidence of a cause-and-effect relationship between the use of oral contraceptives and diseases involving clotting of the blood, Syntex made no mention of these studies in its package insert until May 1968, after plaintiff had stopped taking Norinyl. Moreover, during the relevant time period no mention was made in the Norinyl package insert of the findings of the co-operative rat study with reference to the relationship between oral contraceptives and ocular disorders.

We conclude that there was substantial evidence that Syntex failed to give the medical profession warnings commensurate with its actual and constructive knowledge of the dangers inherent in Norinyl and that the trial court properly permitted the jury to decide the question of **[***34]** Syntex's negligence.

> *Ortho* Warnings on Package Inserts from 12-20-67 **[*403]** when Plaintiff First Took *Ortho-Novum*, through 12-22-68, the Approximate Date on which Plaintiff Last Took *Ortho-Novum*

Various package inserts were published by Ortho during the period in which plaintiff used

Ortho-Novum. Under the heading "clinical laboratory results" on the insert dated December 1967, Ortho cited a report which stated that "the most recent work on the response of blood coagulation factors to oral contraceptives indicated no statistically significant effect."

The December 1967 Ortho-Novum insert also contained the warning which, as discussed above, Dr. Wendel found inadequate to enable the physician to prevent permanent damage to the patient's eyes. [28] Dr. Sutton, one of the ophthalmologists who treated Mrs. McEwen, pointed out another possible defect in this warning. Dr. Sutton testified that when plaintiff visited him in January 1968 he was aware that she had complained on November 25, 1967, of losing sight in her right eye. However, the implication of the warning in question was that medication was to be withdrawn only if an examination revealed papilledema **[***35]** or retinal vascular lesions, even if the patient had previously suffered a partial or complete loss of vision. The January examination did not reveal such abnormalities in plaintiff's eyes, and Dr. Sutton did not advise her to stop taking oral contraceptives at that time.

FOOTNOTES

[28] "Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn."

Moreover, the following information was included in the December 1967 Ortho-Novum package insert:

> "The following occurrences have been observed **[*404]** in users of oral contraceptives. A cause-and-effect relationship has been neither established nor disproved:
>
> "Thrombophlebitis
>
> "Pulmonary embolism
>
> "Neuro-ocular lesions"

Dr. Sutton testified that when he observed retinal hemorrhaging in plaintiff's eyes in December 1968, he relied on such a package insert **[***36]** statement in making his decision not to take plaintiff off birth control pills: "I read it [the insert] very seriously. And if you read it completely you'll read where it says, 'There is no established cause-and-effect relationship.'"

[537]** In addition to those portions of the December 1967 Ortho-Novum package insert which might be misleading or ambiguous, the jury could have found important omissions. For example, this insert, which remained substantially unchanged until June 1968, made no mention of the British studies. Nor was any mention made of the findings of the Ortho-Syntex cooperative rat study as to the effects of oral contraceptives upon the eye, even though a section entitled "animal studies" was included.

Viewing the evidence most favorably to plaintiff, there was substantial evidence to support a jury finding that the December 1967 Ortho-Novum insert was inadequate.

No significant changes were made in the Ortho warnings until the publication of the June 1968 package insert. The June 1968 insert, which remained substantially unchanged until after plaintiff discontinued **[*405]** her use of Ortho-Novum, contained Ortho's first notice to the medical profession **[***37]** of the British studies:

"WARNINGS

"1. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

"Studies conducted in Great Britain and reported in April 1968 estimate there is a seven to tenfold increase in mortality and morbidity due to thromboembolic diseases in women taking oral contraceptives. In these controlled retrospective studies, involving 36 reported deaths and 58 hospitalizations due to 'idiopathic' thromboembolism, statistical evaluation indicated that the differences observed between users and non-users were highly significant.

"The conclusions reached in the studies are summarized in the table below:

[Table omitted]

"No comparable studies are yet available in the United States. *The British data, especially as they indicate the magnitude of the increased risks to the individual patient, cannot be directly applied to women in other countries in which the incidences of spontaneously occurring thromboembolic disease may be different*." (Emphasis **[***38]** ours. Footnotes omitted.)

Dr. Wendel disagreed with the italicized portion of this warning, gave his opinion that the British studies could be applied to American women, and concluded that the information contained in this warning was inadequate.

The June 1968 Ortho-Novum package insert also contained the following information:

"ADVERSE REACTIONS OBSERVED IN PATIENTS **[*406]** RECEIVING ORAL CONTRACEPTIVES

"* * *.

"Although available evidence is suggestive of an association, *such a relationship has been neither confirmed nor refuted for the following serious adverse reactions*:

"* * *

"Neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis

"* * *." (Emphasis ours.)

Finally, the June 1968 insert contained the questionable warning discussed above [29] regarding loss of the patient's vision and failed to mention the pertinent results of the Ortho-Syntex cooperative rat study.

FOOTNOTES

[29] Supra n. 28.

We are unable to hold that the warnings given on the **[***39]** June 1968 Ortho-Novum package insert were, as a matter of law, adequate. The trial court properly submitted this question to the jury.

[538]** In summary, we hold that there existed substantial evidence tending to prove that both Syntex and Ortho were negligent in failing to make warnings to the medical profession which were reasonable in light of each defendant's respective knowledge of the dangers inherent in the use of its oral contraceptive. It remains to be determined whether there was also substantial evidence that the negligence of each defendant was, in fact, a substantial factor in producing the injuries suffered by plaintiff.

Defendants also contend that this case raises a question of proximate cause insofar as there is no substantial evidence that plaintiff's injuries would not **[*407]** have occurred even if adequate warnings had been given. Essentially, defendants contend that there is no evidence that their negligence caused plaintiff's injuries. [30] This argument is more appropriately directed to the issue of causation in fact, and will be considered next.

FOOTNOTES

[30] The gist of this argument is unrelated to foreseeability or culpability. Indeed, defendants do not contend that the intervening negligence of a physician exonerates an ethical drug manufacturer from liability flowing from its failure to warn. Such a contention would be contrary to the better reasoned decisions which have considered the point, usually under the rubric of proximate cause. *E.g.*, McCue v. Norwich Pharmacal Co., 453 F2d 1033 (1st Cir 1972); Sterling Drug, Inc. v. Cornish, 370 F2d 82 (8th Cir 1966); Schenebeck v. Sterling Drug, Inc., 423 F2d 919 (8th Cir 1970); Stevens v. Parke, Davis & Co., 9 Cal 3d 51, 107 Cal Rptr 45, 507 P2d 653 (1973); Krug v. Sterling Drug, Inc., 416 SW2d 143 (Mo S Ct 1967); *see* Restatement (Second) of Torts § 447 (1965). *But see* Oppenheimer v. Sterling Drug, Inc., 7 Ohio App 2d 103, 219 NE2d 54 (1964); Leibowitz v. Ortho Pharmaceutical Corp., 224 Pa Super 418, 307 A2d 449 (1973); Douglas v. Bussabarger, 73 Wash 2d 476, 438 P2d 829 (1968).

Likewise, the mere failure of the physician to read all the drug information sent to him by manufacturers may be foreseeable. *See* Yarrow v. Sterling Drug, Inc., supra n. 25; Merrill, *Compensation for Prescription Drug Injuries*, supra n. 24, 59 Va L Rev at 25, 45, n. 165.

[*40]** III. CAUSE IN FACT

The final element of plaintiff's cause of action is proof that each defendant's failure to warn was, in fact, a substantial factor in producing the damage complained of. Within this broad question of causation, two sub-issues are implicit. First, we must determine whether each defendant's negligence could be found to be a substantial cause of plaintiff's ingestion of the oral contraceptive manufactured by that defendant. If so, we must then decide whether plaintiff's ingestion of that drug could be found to be a substantial factor in producing her ocular injuries.

> A. Whether There was Substantial Evidence that **[*408]** the Failure of Each Defendant to Make Adequate Warnings Regarding the Dangerous Propensities of its Oral Contraceptive was a Substantial Cause of Plaintiff's Ingestion of that Drug?

Defendants ask this court to hold as a matter of law that adequate warnings by them to the medical profession would not have prevented plaintiff's ingestion of their oral contraceptives and, therefore, that their failure to warn did not cause plaintiff's harm. As we understand defendants' thesis, there is no suggestion that doctors would **[***41]** have failed to read adequate warnings or that such warnings, once read, would have been ignored. [31] Rather, defendants contend that for causation to be found, there must be some evidence that if adequate warnings had been given, either plaintiff's prescribing physicians would not have prescribed oral contraceptives in the first place or her treating physicians would have discontinued her use of these drugs in time to avoid her injuries. Defendants assert that there is no evidence as to what any of plaintiff's doctors would have done had there been no negligence.

FOOTNOTES

[31] *Compare* n. 30, supra.

Plaintiff's prescribing physicians did not testify. We need not, however, reach the question of whether there was substantial evidence that a reasonably prudent physician, **[**539]** adequately warned, would not have prescribed oral contraceptives. [32] There was sufficient evidence to permit the jury to find that if adequate **[*409]** warnings had been given, plaintiff's treating doctors probably would have discontinued **[***42]** her use of the drugs in time to avoid permanent injuries.

FOOTNOTES

[32] Plaintiff testified, without objection, that if she had known at the time of prescription that defendants' oral contraceptives might cause circulatory damage, she would not have taken them. While the duty of the ethical drug manufacturer to warn of dangers inherent in its product is a duty owed to the medical profession, rather than to the patient, it is not unlikely that a properly warned physician would discuss such risks with the patient. *See* 21 C.F.R. § 130.45 (b), (c) (1970).

After plaintiff resumed her use of Norinyl in October 1967, she experienced adverse effects which could have been connected by a properly warned treating physician to injuries of the type which she ultimately suffered. On November 25, 1967, Mrs. McEwen notified Dr. Koehler at the Kaiser Hospital that she was losing the sight in her right eye. Plaintiff called Kaiser again on December 17, 1967, and reported that she had been coughing up blood. Both complaints were **[***43]** entered in plaintiff's Kaiser Hospital records, which were received into evidence. Her hospital records also revealed that she had been using Norinyl.

All of the Kaiser physicians who subsequently treated Mrs. McEwen had access to her hospital records. Dr. Bondurant treated plaintiff for coughing up blood at Kaiser on December 18, 1967. Plaintiff returned to Kaiser on December 20, at which time Dr. Tatum changed her prescription from Norinyl to Ortho-Novum. Dr. Sutton, another member of the Kaiser staff who treated plaintiff, testified that he had read the oral contraceptive package inserts before examining plaintiff in January 1968, and that withdrawal of the medication was not recommended if the examination proved normal. Even though he knew that Mrs. McEwen had previously complained of losing sight in her right eye, Dr. Sutton allowed her to continue taking oral contraceptives following the January 1968 examination. Such action was consistent with defendants' warnings. After plaintiff's retinal hemorrhaging had begun, she

returned to Dr. Sutton in December 1968. Again, he failed to advise plaintiff to **[*410]** discontinue use of the pills. Again, the jury could have **[***44]** found that Dr. Sutton relied on the package inserts in making this decision.

Considering this testimony, the gravity of the risk involved, and the evidence of plaintiff's cumulative symptoms, there was substantial evidence that if adequate warnings had been timely given to plaintiff's treating physicians by either defendant, plaintiff's use of the oral contraceptives would have been discontinued before her injuries had become irreversible.

B. Was Each Defendant's Oral Contraceptive a Substantial Cause of Plaintiff's Injuries?

The last link in the chain of defendants' negligence liability is the cause-and-effect relationship between plaintiff's ingestion of defendants' chemically identical pills and plaintiff's ocular injuries. All parties agree that hemorrhaging occurred in plaintiff's retinal blood vessels and that the escaped blood penetrated the vitreous of her eyes, ultimately damaging her vision. The cause of this bleeding is the source of disagreement.

Defendants characterize the plaintiff's theory of the case as a contention that defendants' oral contraceptive pills cause thromboembolic disease, including retinal hemorrhaging. [33] Defendants contend that: **[**540]** **[***45]** (1) hemorrhaging is the exact opposite of clotting and, **[*411]** therefore, plaintiff could not have suffered from a clotting disease; (2) moreover, there is no substantial evidence that plaintiff suffered from a thromboembolic disease of any kind; and, thus (3) the trial court erred in admitting evidence presented by plaintiff relating to diseases involving blood clots.

FOOTNOTES

[33] A clot formed during life in a blood vessel is known as a thrombus; it may or may not obstruct the flow of blood through the vessel. Stedman's Medical Dictionary, supra at 1296. It is unclear whether defendants intend the term "thromboembolic" to include all diseases involving blood clotting. If so, the broader term "thrombotic" might be more appropriate. *Id.* at 1295. Thromboembolic diseases apparently constitute only one class of thrombotic disorders: diseases involving an obstruction or occlusion (closing) of a blood vessel by a thrombus which is dislodged from the vessel wall and transported to the point of blockage. *Id.* at 403, 868, 1295. The term thrombotic disease includes any disease relating to, caused by, or characterized by thrombosis (the formation or presence of a thrombus), regardless of whether the clot is detached from the vessel in which it is formed. *Id.* at 1295.

The record clearly indicates that the plaintiff's theory of the case was not limited to thromboembolic diseases, but also included other diseases involving thrombosis, as well as a narrowing of the vessels unrelated to blood clots.

[*46]** A more accurate description of plaintiff's theory of the case is that the use of defendants' oral contraceptives increased the propensity of plaintiff's blood vessels to form thrombi (clots) or to otherwise narrow. The result was a closing of her retinal vessels -- an occlusion -- and the stoppage of the flow of blood. The culmination of this process was the hemorrhaging which permanently damaged plaintiff's vision.

Plaintiff relied chiefly on the testimony of two experts to causally link her ingestion of defendants' drugs to the bleeding in her eyes. First, plaintiff introduced at trial portions of a deposition taken from Dr. Alice McPherson, a medical professor and treating ophthalmologist specializing in retinal diseases. Based upon her personal examination of plaintiff's eyes, Dr. McPherson testified that plaintiff had suffered from hemorrhaging of the retinal blood vessels.

The damage to plaintiff's vision resulted from the interaction of this escaped blood with the vitreous in her eyes. Eventually the hemorrhaging caused a complete blockage **[*412]** of light in the vitreous of plaintiff's right eye, and thus blindness.

Dr. McPherson stated that the hemorrhaging **[***47]** was the product of an occlusion of the retinal vessels. During a process known as neovascularization, plaintiff's body reacted to the diminished vascular supply to the retina by growing new blood vessels around the occluded area which were abnormal and weak. The seepage of blood through the vessels' fragile walls resulted in the dot hemorrhages and microaneurysms which Dr. McPherson observed. Contrary to defendants' theory that clotting and hemorrhaging are opposites (and therefore somehow mutually exclusive), Dr. McPherson testified that a blood clot can directly cause such bleeding.

During examination by defense counsel, Dr. McPherson gave her opinion as to the immediate cause of the occlusion in plaintiff's eyes:

> "Q You said that occlusion could have been due to thrombosis, but you think it likely wasn't?
>
> "A You see, occlusions are due to -- to occlude something, you either occlude it by pressure or -- pressure from an outside source or pressure from an inside source on a thrombus or emboli, which blows up there. Well, I don't think she had an emboli and I don't think she had blood pressure enough to do it, so I think it would probably be thrombosis. But any narrowing **[***48]** of the blood vessels it becomes occluded, we call it a thrombosis."

The quoted portion of Dr. McPherson's testimony is not a model of clarity. Apparently Dr. McPherson did not believe plaintiff's occlusion to be due either to blood pressure or to emboli (detached clots or other masses occluding blood vessels). [34] However, **[*413]** her testimony can easily be harmonized with plaintiff's theory that the occlusion may have been caused by thrombi (clots which remain attached to the vessel). [35] The quoted testimony could also **[**541]** be interpreted as an opinion that the occlusion resulted either from a thrombus or some narrowing of the vessel unrelated to a blood clot. Either construction is consistent with plaintiff's theory that a thrombus or narrowing of the vessel caused the occlusion. While defendants have pointed out some ambiguity in Dr. McPherson's testimony, this alone is insufficient to overturn the verdict of the jury.

FOOTNOTES

[34] *Id.* at 404.

[35] Earlier in the deposition, Dr. McPherson used the term "thrombosis" when referring to a blood clot in a vein. (Stedman's Medical Dictionary, supra n. 32 at 1295, defines "thrombosis" as the formation or presence of a thrombus.) Dr. McPherson also gave her opinion that "any occlusion can be due to thrombosis."

[*49]** Plaintiff relied on the testimony of Dr. Wendel to demonstrate that her ingestion of defendants' pills caused the thrombotic disorder or other narrowing of the blood vessels which, in turn, injured her eyes. Dr. Wendel testified that one effect of defendants' oral contraceptives on the vascular system is an increase in the propensity of the blood to coagulate in the blood vessel, resulting in occlusion of the vessel by thrombosis. He further testified that these oral contraceptives can occlude a blood vessel without the formation of a

blood clot:

> "[T]he effect [of defendants' oral contraceptives] on the vascular system is not just increasing the propensity of the blood to coagulate in the vessel. It can also be changes in the vessel wall, of blood vessels. This means particular thickening of the vessel -- of the lining of the vessels. And by increasing the thickness, narrowing the diameter of the vessel so less blood, or no blood at all, can go through. It results in the same clinical symptom, **[*414]** no blood supply, but is something in addition to the formation of a thrombus."

Dr. Wendel concluded that the occlusion and neovascularization in plaintiff's **[***50]** eyes were caused by her ingestion of defendants' birth control pills:

> "A In my opinion, based on the study of the medical records cited by you, the intake of the oral contraceptives Norinyl and Ortho-Novum was the most probable cause of Mrs. McEwen's eye maladies, right and left eye.
>
> "Q Would you please explain your answer, Doctor.
>
> "A The retinal changes found by the ophthalmologists in the retinas of Mrs. McEwen -- there is neovascularization, microaneurysms, dot hemorrhages, massive hemorrhages in the retina and into the vitreous body, detachment of the retinas and holes in the retinas called Eale's disease or retinitis proliferans -- are known, or these changes are known to be connected or associated with various diseases or conditions. There is no one particularly specific cause known which would characteristically cause these changes. Therefore I looked in the records for those causes which, over time, have been considered with more or less evidence as possible causes of these kinds of eye changes, * * *.
>
> "* * *.
>
> "Taking everything together and balancing the various pieces of evidence, there is no indication for tuberculosis; no indication for lupus; no indication **[***51]** for sickle cell anemia. Sarcoidosis -- the possibility that sarcoidosis could have been the cause is extremely remote. So what remains is hypertension, probably caused or causally connected with the intake of oral contraceptives; chemical diabetes, most likely caused by the intake of oral contraceptives; and the oral contraceptives themselves, that means by direct action on the blood and/or the blood vessels in the eye. Taking these altogether, **[*415]** on balance, in my opinion, the preponderance of evidence points to oral contraceptives as the most probable cause." [36]

[542]** Thus, Dr. Wendel supplied the connective link between the plaintiff's physical condition, as observed by Dr. McPherson, and the plaintiff's use of defendants' drugs. [37]

FOOTNOTES

[36] "* * * For medical opinion testimony to have any probative value, it must at least advise the jury that the inference drawn by the doctor is more probably correct than incorrect. If the probabilities are in balance, the matter is left to speculation. * * *" Crawford v. Seufert, 236 Or 369, 375, 388 P2d 456, 2 ALR3d 354 (1964). Defendants contend that although Dr. Wendel testified that their oral contraceptives were the "most probable cause of Mrs. McEwen's eye maladies," he admitted considering other "possible

causes" in arriving at this conclusion, and therefore his opinion was actually based on mere possibilities.

Dr. Wendel did state that seven diseases or conditions are known in medicine to be associated with the type of retinal changes found in Mrs. McEwen's eyes. However, he then proceeded to explain that four of these "possible" causes were probably unrelated to plaintiff's injuries, in light of the current state of medical knowledge and the results of plaintiff's laboratory tests. The remaining three possibilities were all causally connected by Dr. Wendel to plaintiff's use of oral contraceptives.

On direct and cross-examination, Dr. Wendel's conclusions as to causation were consistently expressed in terms of probability, not possibility. This contrasts sharply with the equivocal, inconsistent medical testimony which we found insufficient in Howerton v. Pfaff, 246 Or 341, 425 P2d 533 (1967). Furthermore, Dr. Wendel's opinion was based on, and supported by, his systematic analysis of the evidence in the case, unlike the expert opinion given in Wintersteen v. Semler, 197 Or 601, 250 P2d 420, 255 P2d 138 (1953). We conclude that Dr. Wendel's expert opinion showed with reasonable certainty the requisite causal connection between plaintiff's ingestion of defendants' oral contraceptives and her subsequent ocular injuries. The law requires no more. **[***52]

37 While Dr. Wendel was of the opinion that defendants' oral contraceptives gave rise to plaintiff's ocular disorder, Dr. McPherson was unable to identify the underlying cause of this disease. Describing plaintiff's condition as "very puzzling and unusual," Dr. McPherson diagnosed it as "retinitis proliferans [neovascularization of the retina extending into the vitreous (Stedman's Medical Dict., supra n. 2 at 1094)], cause unknown."

Although Dr. McPherson testified that blood clotting and hypertension are side effects caused by oral contraceptives, she was of the opinion that defendants' birth control pills had not caused plaintiff's injuries. This conclusion was based on Dr. McPherson's belief that plaintiff's condition had originated before she began taking oral contraceptives. In a letter dated December 19, 1969, Dr. McPherson stated:

> "Although the etiology of this condition is unknown, and our records do not show the period of time during which the patient took the oral contraceptives, it is my opinion that this ocular pathology is of long standing, and probably started when the patient was much younger and before the introduction of the birth control pills to the market."

At her deposition, however, Dr. McPherson was equivocal as to the date of origin. She testified that plaintiff's malady had existed for a period of time that "wasn't weeks and * * * wasn't months * * *. The exact time of onset would be relatively unknown." She also had the "feeling" that the disease was "many, many years" old, but later testified that the abnormal growth of new blood vessels in plaintiff's eyes was a "few years" old and that she could not be specific. Still later, she testified that she could not decide precisely when the hemorrhage had occurred in plaintiff's right eye; nor could she determine the time when the abnormal growth of blood vessels began, because "you can't pinpoint the time when you see it at a later stage." As for plaintiff's left eye, Dr. McPherson was able only to determine that the occlusion "was of longer standing than just a few weeks or a few months * * *." At a later point in the deposition Dr. McPherson expressed her belief that the clotting in plaintiff's right eye originated "quite a few years ago." Yet her final opinion was that the growth of new vessels in plaintiff's eyes "just looked like it didn't happen in the last three weeks."

Contradicting the testimony of Dr. McPherson on this point, Dr. Sutton testified that when he examined plaintiff in December, 1968, he was of the opinion that her retinitis

proliferans had developed "most likely within the past year."

Considering all of the testimony in the light most favorable to plaintiff, it was permissible for the jury to find that plaintiff's disease originated after she began to take birth control pills in 1966.

[*53]** In summary, substantial evidence supported the following elements of causation in plaintiff's theory of the case:

> (1) The impairment of plaintiff's vision was **[*416]** caused by bleeding which extended into the vitreous portion of her eyes.
>
> (2) This hemorrhaging was the result of a proliferation of fragile new blood vessels which developed **[*417]** following an occlusion of plaintiff's normal retinal blood vessels.
>
> (3) The occlusion of plaintiff's blood vessels was probably due to narrowing **[**543]** of the plaintiff's blood vessels or to thrombosis.
>
> (4) Defendants' oral contraceptive pills caused this narrowing of the vessels or thrombosis in the plaintiff's eyes.

It is true that defendants presented contrary evidence on many of these points. However, where the factual determinations of the jury are supported by substantial evidence, as they are here, they will not be disturbed.

Defendant Syntex makes an additional and independent causation argument: Norinyl could not have been a substantial factor in causing plaintiff's harm because her ultimate injuries did not occur until a year after she discontinued use of that drug. Syntex contends that any adverse **[***54]** effects plaintiff experienced from her use of Norinyl were not irreversible and would certainly have subsided by the time plaintiff's hemorrhaging began. In support of this argument, Syntex points out that when plaintiff discontinued her use of Norinyl for three months in 1967 the symptoms of her adverse effects abated. Moreover, when Dr. Sutton examined Mrs. McEwen in January 1968 -- after she had stopped taking Norinyl -- he found no evidence of a visual problem except for bilateral exophthalmos (bulging eyeballs). Syntex places special emphasis on the following testimony of Dr. Wendel:

> "Q [I]f [plaintiff] had stopped in December **[*418]** of '67 and not taken the pill after that, then there would have been no further difficulty as a result of the pill?
>
> "* * *.
>
> "A Further development. Most likely not. I won't say for certain, but most likely not."

Syntex concludes that there was neither any evidence that plaintiff suffered a retinal hemorrhage while using Norinyl nor any evidence that her injuries were irreversible when she discontinued her use of that drug. It does not, however, necessarily follow that Syntex is not liable for Mrs. McEwen's harm.

The **[***55]** respective liability of multiple defendants depends upon whether the negligence of each was a substantial factor in producing the complained of harm. If both Syntex and Ortho were negligent and their negligence combined to produce plaintiff's injuries, then the negligence of Ortho was concurrent with that of Syntex and does not insulate Syntex from liability. *Hills v. McGillvrey*, 240 Or 476, 402 P2d 722 (1965). This is true although the negligent omissions of each defendant occurred at different times and without concerted action. *Kuhns v. Standard Oil Co.*, 257 Or 482, 478 P2d 396 (1971). *See also Murray v. Helfrich*, 146 Or 602, 30 P2d 1053 (1934). Nor is it essential to Syntex's liability that its negligence be sufficient to bring about plaintiff's harm by itself; it is enough that Syntex substantially contributed to the injuries eventually suffered by Mrs. McEwen. *See Escobedo v. Ward*, 255 Or 85, 464 P2d 698 (1970).

Assuming arguendo that the evidence was insufficient to entitle the jury to find that plaintiff's injuries were irreversible at the time she stopped taking **[*419]** Norinyl, there was ample evidence that plaintiff's ingestion of Norinyl substantially **[***56]** increased the risk of such harm and that the combined effect of Norinyl and Ortho-Novum was the damage to her eyes. Plaintiff took Norinyl from December 3, 1966, until July 1967, and then discontinued her use of oral contraceptives for three months. In October 1967 she resumed her use of Norinyl, and in November 1967 she called the Kaiser Hospital and complained of losing sight in her right eye. She continued taking Norinyl until December 20, 1967, when she changed to Ortho-Novum oral contraceptives. Plaintiff used Ortho-Novum from that date until late December 1968, by which time her retinal hemorrhaging had begun. Norinyl and Ortho-Novum are chemically identical.

There was expert testimony to the effect that the abnormal growth of new blood vessels in plaintiff's eyes resulted from a gradual process. That the effects of the oral contraceptives are cumulative in nature **[**544]** is substantiated by the fact that Mrs. McEwen's retinal hemorrhaging did not begin until approximately one year after she began using Ortho-Novum. Dr. Wendel concluded that "the intake of the oral contraceptives *Norinyl and Ortho-Novum* was the most probable cause of Mrs. McEwen's eye maladies, **[***57]** right and left eye." (Emphasis ours.) The lapse of time between the date plaintiff ceased using Norinyl and the time when her injuries culminated was merely another factor for the jury to consider in resolving the causation issue. *See American Insurers v. Bessonette*, 235 Or 507, 384 P2d 223, 385 P2d 759 (1963).

We conclude that there was substantial evidence that both Norinyl and Ortho-Novum, as taken by Mrs. **[*420]** McEwen, were substantial factors in producing her injuries.

It remained for plaintiff to prove the amount of her damages. Defendants assign error to the admission of expert testimony concerning the amount of plaintiff's future economic loss resulting from her ocular injuries. Dr. Bassett, a professor of economics at the University of Washington, testified in response to plaintiff's hypothetical question. In its original form, the hypothetical assumed plaintiff's total disability, but upon objection it was amended to assume only that "Mrs. McEwen has a permanent injury to both eyes, one of which is blind and the vision in the other eye has been impaired." The assumption of these injuries was supported by ample evidence in the case, and the hypothetical question, **[***58]** as modified, was proper.

Although Dr. Bassett answered only the altered form of the hypothetical question, he admitted upon cross-examination that in calculating his answer he had assumed that Mrs. McEwen did not have the ability to work again. After the basis of Dr. Bassett's testimony had been disclosed, counsel for defendants did not move to strike his testimony concerning the amount of plaintiff's future economic loss. On appeal, defendants now contend that because there was no evidence of Mrs. McEwen's total disability, the trial court erred in permitting Dr. Bassett to give an opinion as to the amount of plaintiff's future pecuniary loss based on the assumption that she would not be able to work again.

It is well settled that the facts assumed by an expert must be supported by evidence in the record, "for the reason that a jury must determine the weight to be given the [expert's] opinion, and, without **[*421]** knowledge of what facts the expert accepts as true, an evaluation of his opinion is impossible." *Devine v. Southern Pacific Co.*, 207 Or 261, 273, 295 P2d 201 (1956); *cf.* McCormick, Evidence 33 (2d ed 1972). However, it is equally well established that **[***59]** "a motion to strike improper testimony must be made as soon as the ground for such a motion is disclosed." *Wallender v. Michas*, 256 Or 587, 592, 475 P2d 72 (1970), and that an objection to proffered evidence not made in the trial court will not be considered for the first time on appeal.

We note that the cross-examination of Dr. Bassett explicitly informed the jury of his assumption of plaintiff's total disability. Moreover, the trial judge instructed the jury that there was "no evidence of total disability" in the case. These circumstances tended to minimize any potential harm to defendants resulting from Dr. Bassett's assumption of a fact not in evidence.

CONCLUSION

In summary, substantial evidence supports the trial court's submission of this case to the jury. To further protract this opinion by discussing each of defendants' remaining assignments of error would be unproductive; we have carefully reviewed each contention and find no reversible error.

Therefore, the judgment of the trial court is affirmed.